REMARKS

Claims 20, 49, 51, 57, 59 and 65-69 previously were pending in the subject application. New dependent claims 70 and 71 are hereby added. Claim dependencies of claims 49, 51, 57, 59, 66, and 67 have been changed to depend from claim 70 or 71. These amendments add no new matter and find support in the application as published at least at paragraphs 0007-0015, 0031, 0032, 0036, 0079-0089, 0112, 0120, 0128, and 0169-0170. Applicants hereby resubmit below (in part II) the arguments set forth in the Reply filed April 21, 2010. Applicants respectfully request that the Examiner enter this Response and consider the following remarks.

I. Preliminary Remarks

The discussion and arguments set forth in section II below were previously filed and considered by the Examiner but were not entered because, according to the Advisory Action (May 11, 2010), the response failed to satisfy 37 C.F.R. § 1.116(e) (Advisory Action at 1) and/or because it failed to put the application in condition for allowance (*id.* at 2). Applicants contend that Rule 116 was satisfied because Applicants clearly stated in their response that the Examiner "appears to have been persuaded by Applicants' response to the [previous] obviousness rejection, and has set forth a different basis for rejecting the claims as obvious over the same asserted references." Amendment at 5 (April 21, 2010). This is clearly why Applicants' "evidence" (consisting primarily of a response to the newly-presented obviousness rejection) presented in the amendment was both necessary and not presented earlier. It was necessary to respond to the new basis for rejecting the claims, and it was not earlier presented because the rejection to which it responded was not presented earlier. *See* 37 C.F.R. § 116(b)(3) (it is believed that 37 C.F.R. § 1.116(e), cited in the Advisory Action, is not applicable because the Amendment was not accompanied by an affidavit or other evidence; rather, the Amendment "touch[ed] the merits of the application" (37 C.F.R. § 1.116(b)(3)).

Further, Applicants disagree that the amendment fails to put the application in condition for allowance. The Examiner's basis for not being persuaded by Applicants' response appears to specifically rely on a reference that does not qualify as prior art, Qu *et al.*, *Expression and Function of a Biological Pacemaker in Canine Heart*, Circulation 107: 1106-1109 (originally

published online February 24, 2003).[1] The Advisory Action states the following:

> [G]iven that HCN2 gene was routinely over expressed for improving conduction disturbance in heart by inducing pacemaker current (see Qu et al page 1108, col. 2, last two para), it would have been a matter of design choice for one of ordinary skill in the art to combine different transgene each of which is taught by the prior art to be useful for the same purpose of improving cardiac disturbance in order to produce a new composition that is to be used for the very same purpose.

Advisory Action at 3 [emphasis added].

Qu does not qualify as prior art because it was published on February 24, 2003, after the present application's priority date of January 15, 2003, the filing date of U.S. Provisional Application No. 60/440,265, to which this application claims priority. It should be noted that, even though the combined declaration and power of attorney in this application indicates that U.S. 60/440,265 was filed on "January 15, 2004," the first page of the conventional application's specification correctly identifies the provisional application number and date. Further, the USPTO's bib data sheet acknowledges that "This appln claims benefit of 60/440,265 01/15/2003," and the claimed benefit is initialed by the Examiner and the bib data sheet is signed by the Examiner. Because the relied-upon Qu article does not qualify as prior art, the obviousness rejection articulated in the Advisory Action should be withdrawn.

In a telephone discussion with Examiner Singh on July 20, 2010, the undersigned requested clarification regarding citation of the Qu (2003) reference. Examiner Singh indicated that Qu (2003) was inadvertently cited in the Advisory Action and that the rejection set forth in the final Office Action rests on the Lee and Qu (2001) references. The Examiner indicated that the Advisory Action reiterates the rejection set forth in the final Office Action. The undersigned is grateful to the Examiner for the courtesy of this discussion.

Part II of this response, below, re-states the arguments set forth in the amendment filed April 21, 2010 in response to the office action dated January 21, 2010. Additional comments in

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[1] The improperly relied-upon Qu (2003) article should not be confused with a different Qu article cited in the previous Office Action and in the Advisory Action, which was published in 2001 (Qu *et al.*, *HCN2 Overexpression in Newborn and Adult Ventricular Myocytes: Distinct Effects on Gating and Excitability*, Circ. Res. 89: e8-e14 (2001)).

response to the Advisory Action are set forth in Part III, below.

II. Rejections and Responses

In the previous office action (dated April 29, 2009), the Examiner rejected the claims as then pending on enablement, obviousness, and non-statutory obviousness-type double-patenting grounds. Applicants contested the enablement and obviousness rejections on the merits and further amended the claims, and argued that a terminal disclaimer was not then appropriate since the double-patenting rejection was provisional. In the pending office action (dated January 21, 2010), the Examiner has withdrawn the enablement rejections in view of the amended claims. As detailed below, the Examiner also appears to have been persuaded by Applicants' response to the obviousness rejection, and has set forth a different basis for rejecting the claims as obvious over the same asserted references. The obviousness-type double-patenting rejection maintained in the pending office action was withdrawn in view of Applicant's terminal disclaimer filed April 21, 2010. *See* Advisory Action at 2. Applicants argue that the pending rejections should be withdrawn for the reasons set forth below.

A. 35 U.S.C. § 103

Rejection

The Examiner has rejected claims 20, 49, 51, 57, 59, and 65-68 as allegedly obvious over U.S. Patent No.7,494,644 ("Lee") and Qu et al. (Circ. Res. 89: e8-e14, at e9 (2001), of record). Applicants understand that the rejection is intended to apply as well to dependent claim 69, which was added in the previous amendment. According to the Examiner, Lee teaches compositions that comprise mammalian cells such as mesenchymal stem cells ("MSCs") "genetically engineered to express connexin 43 (Cx43) protein intended for establishing electrical coupling between cardiomyocytes" and the recombinant cells. Office Action at 3. According to the Examiner, Lee also teaches a "method of establishing electrical coupling between cardiomyocytes and recombinant mammalian cells" engineered to express Cx43 protein. *See id.* at 3. The Examiner recognizes that "electrical coupling" "allows for intracellular communication" so as to provide for "electrical conduction between the cells." *See*

id. The Examiner further states that Lee discloses a method that uses such recombinant cells to "establish an electrical connection between the recombinant cell" and a host myocardial cell in order to treat "a cardiac conduction disturbance in a host." *See id.* at 3-4. The Examiner concedes that Lee does "not disclos[e] MSC comprising nucleic acid encoding HCN2." *Id.* at 4.

According to the Examiner, Qu et al. discloses that treatment of adult and neonatal cells in culture with an "adenoviral construct comprising nucleic acid encoding HCN2" "resulted in expression of high current levels, with faster activation in neonate." *See* Office Action at 4.

The Examiner considers Qu et al. to compensate for the acknowledged deficiency of Lee. The pending rejection relies on a rationale different than that of the previous rejection. The previous rejection was based on an alleged motivation to modify Lee by replacing a nucleic acid encoding Cx43, used by Lee, "with another gene such as HCN2." *See* Office Action (April 29, 2009) at 8. The Examiner appears to have been persuaded by Applicants' argument in the previous amendment that the person of ordinary skill in the art would not have been motivated to make such a substitution. The pending rejection thus is based on an alleged motivation to modify Lee, not by replacing Cx43 with HCN2, but by including a nucleic acid encoding HCN2 in addition to the nucleic acid encoding Cx43. According to the Examiner,

> [i]It would have been obvious for one of ordinary skill in the art at the time of invention to modify the composition disclosed by Lee by including the gene of interest HCN2 as disclosed by Qu. One of ordinary skill in the art would be motivated to do [sic] use HCN2 as Qu had already shown that HCN2 could be expressed in mammalian cells to induce pacemaker current.

Pending Office Action at 4. *See also id.* at 5 (stating that Applicants' claimed composition comprises any MSCs incorporated with a nucleic acid that encodes HCN2, including MSCs that are further genetically modified with, e.g., a nucleic acid encoding Cx43).

The Examiner further states that the person of ordinary skill in the art would reasonably have expected such MSCs to form gap junctions when administered to the heart because "Lee taught hMSCs engrafts in the myocardium and forms gap junction with recipient MCS." *Id.* at 4.

Response

Applicants believe that the pending claims should be allowed because the claims should not be considered obvious on the grounds set forth by the Examiner. As detailed below, there is no teaching or suggestion in either cited reference to include an additional nucleic acid encoding HCN2 in the hMSCs of Lee. Further, Lee in fact teaches away from including an additional nucleic acid. Consequently, the cited Lee and Qu references, taken alone or in combination, do not render the claims *prima facie* obvious.

No motivation to modify Lee

Claims 20, 49, 51, 57, 59, and 65-69 would not have been *prima facie* obvious on the grounds set forth by the Examiner because the person of ordinary skill in the art would not have been motivated to modify Lee's disclosure as the Examiner proposes. As the Examiner recognizes, Lee teaches "methods for establishing electrical coupling between cardiomyocytes and recombinant cells which have been genetically engineered to express a connexin protein such as connexin 43 (Cx43) protein." Lee at col. 3, ll. 25-28. Further, Lee's purported "invention is based on the discovery that genetic modification of skeletal muscle cells to express a recombinant connexin, enables the genetically modified cells to establish electrocommunication with cardiac cells via gap junctions." *Id.* at col. 3, ll. 28-32 (emphasis added). Further, according to Lee, "[p]roduction of connexin in the recombinant cell provides for an electrical connection." Lee at col. 11, ll. 1-2. Lee focuses on the use of skeletal muscle cells for contractility; Lee teaches that such cells should be transformed with connexins to establish electrical connections with cardiac cells.

Further, the secondary Qu et al. reference does not cure the deficiencies of Lee, acknowledged by the Examiner to be Lee's failure to teach or suggest the incorporation of an HCN-encoding nucleic acid into the cells introduced into the heart. Qu et al. simply attempts to provide an explanation for the observed phenomenon that "[v]entricular pacemaker current (I_f) shows distinct voltage dependence as a function of age, activating outside the physiological range in normal adult ventricle, but less negatively in neonatal ventricle" even though "heterologously expressed HCN2 and HCN4, the putative molecular correlates of ventricular I_f, exhibit only a modest difference in activation voltage." Qu et al. at e8. The authors conclude

that "the developmental difference in pacemaker current voltage dependence under our experimental conditions is largely accounted for by an effect of the myocyte maturational state on the HCN2 isoform." *Id.* at e12.

Qu et al. thus does not discuss mesenchymal stem cells or their use to deliver genes to the heart or to treat a cardiac rhythm disorder or induce a current in a heart. Specifically, Qu et al. does not teach or suggest that a nucleic acid encoding an HCN can be delivered to a heart via a mesenchymal stem cell. Rather, the only expression experiments discussed by Qu et al. entail infection of rat ventricular myocytes with an adenoviral construct comprising an HCN2-encoding DNA fragment. The deficiency of Lee, recognized by the Examiner, thus is not cured by Qu et al.; Qu et al. would not have motivated the person of ordinary skill in the art to modify Lee to arrive at the claimed compositions or methods.

Lee teaches away from the modification asserted by the Examiner

According to the current office action, Lee teaches that the cells used according to Lee's disclosure can be transfected with an additional nucleic acid, citing Lee at column 13, line 10. Office Action at 6. The cited passage, however, undermines the Examiner's argument and supports the Applicants' position. The cited passage reads as follows:

> The recombinant cells can optionally be genetically modified to express other proteins, such as N-cadherin protein. However, the cells are preferably are [sic] not so modified so as to avoid additional genetic manipulation of the cell to be transplanted. Furthermore, the recombinant cell need not be modified to express or overexpress N-cadherin, as the inventors here have shown that expression of an exogenous (e.g., introduced or recombinant) connexin (either in the presence or absence of expression of any endogenous connexin) is sufficient.

Lee at col. 13, ll. 10-19.

This passage reveals two flaws in the Examiner's argument. First, to the extent that Lee teaches that the cells can be genetically modified, Lee provides no suggestion that the other genes should encode a protein relevant to pacemaking. To the contrary, Lee suggests a gene that encodes N-cadherin, which, like connexin 43 that Lee introduces into cells, is involved in cell-cell connection. *See, e.g.*, Lee at col. 11, ll. 5-20 and Bruce Alberts *et al.*, Molecular Biology of

the Cell 966 (3d ed. 1994) ("Alberts") ("The cadherins are responsible for Ca^{2+}-dependent cell-cell adhesion in vertebrate tissues."). There is thus no teaching or suggestion to modify Lee's disclosure by introducing a nucleic acid wholly unrelated to the aim of Lee. Lee aims to "effect cardiac repair" by transplanting (into the heart) cells that electrically couple to endogenous cardiomyocytes. *See* Lee at col. 3, ll. 17-21. Lee therefore only suggests using nucleic acids related to achieving electrical coupling. *See* Lee at col. 3, ll. 6-10 (stating that "N-cadherin and connexin 43 were both detected at the contact sites between cardiomyocytes and skeletal myotubes" in an in vitro study). Such a limited suggestion would not encompass the use of other nucleic acids, such as a nucleic acid that encodes HCN2. The person of ordinary skill in the art therefore would not have been motivated to combine Lee with a reference such as Qu that is concerned with nucleic acids that encode proteins unrelated to electrical coupling of cells.

Second, the very passage the Examiner cites actually teaches that further genetic modification is optional but that "the cells are preferably are not so modified." Lee thus actively discourages genetic manipulation of the cells other than to incorporate a connexin. Lee therefore teaches away from incorporating the cells with an additional nucleic acid, such as a nucleic acid that encodes HCN2. That it is preferred "to avoid additional genetic manipulation of the cell" (Lee at col. 13, ll. 12-14) suggests that such manipulation might interfere with the desired results. Lee's teaching is therefore contrary to the Examiner's contention that Lee suggests incorporating into the stem cells a nucleic acid in addition to the Cx43-encoding nucleic acid, and that that nucleic acid could encode HCN2. *See, e.g.*, *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986) (finding that the prior art leads away from the claimed invention, reasoning that "'[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art'" (quoting *In re Wesslau*, 353 F.2d 238, 241)) and *In re Baird*, 16 F.3d 380, 382-83 (Fed. Cir. 1994) (stating that the Knapp reference "appears to teach away from the selection of bisphenol A by focusing on more complex diphenols . . . . Fifteen typical diphenols are recited. None of them, or any of the other preferred phenols recited above, is or suggests bisphenol A.").

Further, Qu would not have provided a motivation to add a nucleic acid encoding HCN2

to Lee's connexin-expressing cells because, as noted above, Qu was strictly concerned with explaining a natural phenomenon and not with any potential clinical uses of HCN2. The mere discussion of HCN2 or its pacemaking properties should not be considered motivation to use it in Lee's cells, which are intended merely to achieve electrical connectivity with the cells of the heart into which they are transplanted, particularly when Lee leads away from any such modification.

III. Additional Comments

In response to the arguments set forth in the Advisory Action, Applicants wish to emphasize that no *prima facie* obviousness should be found in view of the above and the following points:

- the Lee reference is solely concerned with effecting repair of cardiac tissue by transplanting, into the heart, cells that can form functional gap junctions (by virtue of carrying a connexin 43 transgene), the repair being effected solely as a consequence of the resulting establishment of electrocommunication with cardiac cells via gap junctions (*see, e.g.*, Lee at col. 3, ll. 25-35, col. 4, ll. 14-23);

- only impermissible hindsight leads to the addition of an HCN2 transgene to the connexin 43-expressing cells of Lee;

- as noted above, the second Qu reference, page 1108 of which is cited by the Examiner in the Advisory Action, is not prior art and therefore cannot be relied upon to demonstrate that use of an HCN2 transgene "would have been a matter of design choice" (Advisory Action at 2);

- the Examiner does not assign appropriate weight to Lee's clear teaching away from "additional genetic manipulation of the cell to be transplanted" (*see* Lee at col. 13, ll. 10-14).

Lee is concerned with solving the known problem that "[p]revious attempts to transplant skeletal muscle cells into myocardium have lacked the electrical coupling to cardiac cells which

is necessary for myocardial coordinated activity." *Id.* at col. 2, ll. 62-65. "Cardiomyocytes are electromechanically coupled by intercalated disks composed of adherens and gap junctions." *Id.* at col. 2, ll. 29-30. The gene product known to form cardiomyocyte gap junctions is connexin 43 ("Cx43"). *See id.* at col. 2, ll. 31-33. The gene product known to form cardiomyocyte adherens junctions is N-cadherin. *See id.* Lee proposes to "induc[e] and enhanc[e] [the] electrical coupling between cardiomyocytes and transplanted cells." *See id.* at col. 3, ll. 17-21. Lee states that:

> In another aspect, the invention features a method for treating a cardiac conduction disturbance in a mammalian host, the method comprising introducing into cardiac tissue of the host a therapeutically effective amount of a skeletal muscle cell genetically modified to express a recombinant connexin 43 protein, where introducing is effective to establish an electrical connection between the introduced recombinant skeletal muscle cell and a myocardial cell of the host cardiac tissue, thereby treating the cardiac conduction disturbance.
>
> *Id.* at col. 4, ll. 31-39 (emphasis added).

Similarly:

> The present invention thus provides methods for using a recombinant cell genetically modified to produce a connexin protein to produce persistent functional gap junctions between the recombinant cell and cardiomyocyte to obtain electrical communication between these cells. The use of recombinant cells that express recombinant Cx43 (or other connexin protein) increases and maintains the communication between the recombinant cells and myocardial cells, thus providing improved and coordinated electrical coupling with increased efficacy of myocardial contractility. The present invention provides methods of treatment of cardiac disease by transplanting or grafting recombinant cells modified to express a connexin into cardiac tissue to effect myocardial repair. Congestive heart failure is an exemplary cardiac disease that can be treated according to the methods of the invention.
>
> *Id.* at col. 6, l. 55-col. 7, l. 3 (emphasis added).

It is therefore apparent that Lee is not concerned with "treating cardiac rhythm disorder" generally (*see* Advisory Action at 2), but rather with treating cardiac conditions in which the provision to the heart of additional cells that can become electrically connected to the native cardiomyocytes can alleviate the condition. Since such cells (without more, and Lee does not teach more) do not provide pacemaker activity, the person of ordinary skill in the art would not

have been motivated to apply Lee's disclosure to treatment of a condition characterized by defective pacemaking, contrary to the Advisory Action. Thus, only impermissible hindsight would have led to the use of an HCN2 transgene in the cells of Lee. In the absence of hindsight, the mere knowledge that HCN2 can generate pacemaker current in vitro as set forth in Qu (2001) would not have led to the incorporation of HCN2 into Lee's cells or methods.

Lee's disclosure thus is limited to the provision of cells modified to express Cx43 in order to treat a conduction disturbance, thereby "improving conduction in the heart." *See* Lee at col. 15, l. 67-col. 16, l. 1. Since Lee is concerned with improving conduction, and the transplanted cells are capable of improving conduction by virtue of expressing a Cx43 transgene, Lee's method requires the Cx43 transgene. The only other transgene specifically suggested by Lee is one that could further enhance electromechanical connectivity between the transplanted cells and the heart cells, N-cadherin (see discussion above). Since Lee is concerned with establishing electrochemical connectivity between transplanted cells and endogenous heart cells, and such connectivity is sufficient to achieve Lee's treatment goals, there is no suggestion, motivation, or reason to modify Lee's express teaching by use any additional transgene other than one that would enhance or promote electrochemical connectivity. This would not include HCN2.

Further, Lee also states that any "additional genetic manipulation" is "preferably" avoided, the implication being that the cells to be transplanted could be compromised by such manipulation.. *See id.* at col. 13, ll. 10-18. The Advisory Action does not attribute appropriate weight to this teaching away, attempting to limit it to referring to the use of an additional N-cadherin transgene. *See* Advisory Action at 2 and 3. But Lee is not so limited in its teaching away. It generally states that additional genetic manipulation should be avoided without any qualification, and gives a general reason for avoiding such additional manipulation. *See In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986) (stating that "the prior art as a whole must be considered").

IV. Information Disclosure Statement

An information disclosure statement ("IDS") accompanies this amendment. The IDS includes certain references that the Japanese Examiner cited as prior art against claims pending

in the corresponding Japanese Application No. 2006-500957 (the remaining references that the Japanese Examiner cited as prior art against the pending claims were previously made of record in this case). It also includes certain office actions from U.S. Patent Application No. 10/342,506, which shares a specification in common with the instant application.

CONCLUSION

In view of the remarks made hereinabove, Applicants respectfully request that the Examiner reconsider and withdraw the pending rejections and earnestly solicit allowance of the now pending claims.

If a telephone interview would assist in expediting prosecution of the subject application, the Examiner is invited to telephone the undersigned at the number provided below. No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 11-0600.

Respectfully submitted,

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